Inhaled Prostacyclins: Treprostinil (Tyvaso™) and Iloprost (Ventavis®)

Criteria for Use

September 2011

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. ***THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Product Information should be consulted for detailed prescribing information. The VA National PBM-MAP-VPE Treprostinil Inhalation Drug Monograph and Pharmacologic Management of Pulmonary Arterial Hypertension documents are available at www.pbm.va.gov or http://vaww.pbm.va.gov.

INCLUSION CRITERIA

All of the following must be selected for patient to be eligible:

- ❑ Definitive diagnosis of Pulmonary Arterial Hypertension (PAH) confirmed by right-heart catheterization including hemodynamic diagnosis: mean pulmonary artery pressure (mPAP) >25 mmHg and pulmonary capillary wedge pressure (PWCP) or left ventricular end diastolic pressure (LVEDP) ≤15 mm Hg
- ❑ World Health Organization (WHO) Group 1[a] PAH
- ❑ Under the care of an experienced provider in the management of PAH
- ❑ Not a candidate for continuous prostacyclin infusion therapy
- ❑ Patient is treated with or has been assessed for adjunct therapies such as oxygen, diuretics, digoxin and warfarin
- ❑ Patient with NYHA Functional Class III[b] symptoms who is not a candidate for or remain symptomatic despite therapy with an endothelin receptor antagonist ([ERA]; e.g., ambrisentan, bosentan) or phosphodiesterase-5 (PDE-5) inhibitor (e.g., sildenafil, tadalafil) or patients with NYHA Functional Class IV[b] symptoms

Note:

- *Efficacy of iloprost has been established primarily as monotherapy in PAH treatment naïve patients. Small studies evaluating iloprost as add-on therapy in patients on bosentan or sildenafil have yielded mixed results.*
- *Treprostinil inhalation has only been studied as add-on therapy in patients already on an ERA or PDE-5 inhibitor. In the pivotal phase III study, treprostinil inhalation was associated with a modest improvement in 6-minute walking distance (6MWD), with a greater effect found in patients with a lower baseline 6MWD.*
- *Evidence for the use of inhaled prostacyclins in patients with NYHA Functional Class IV[b] symptoms is very limited; continuous prostacyclin infusion therapy is typically preferred in these patients.*

If applicable, the following must be selected for patient to be eligible:

- ❑ If acute vasoreactivity test positive, calcium channel antagonist therapy has been tried unless right heart failure is present

DOSAGE AND ADMINISTRATION

- **Treprostinil:** 3 to 9 breaths (18-54 mcg) during waking hours 4 times daily, about 4 hours apart.
- **Iloprost:** 2.5 to 5 mcg 6 to 9 times daily, at least 2 hours apart. Note: the 10 mcg/ml strength may be used for the 2.5 or 5 mcg dose; the 20 mcg/ml strength should only be used for the 5 mcg dose and reduces administration time.

ISSUES FOR CONSIDERATION

- **Airway Irritation:** Inhaled prostacyclins are associated with airway irritation and have not been evaluated in patients with underlying lung disease (e.g., chronic obstructive pulmonary disease [COPD], asthma, advanced interstitial lung disease). Use of inhaled prostacyclins in these patients should be done with caution in the absence of safety data. Increased cough was also frequently reported with inhaled iloprost during clinical trials. Treprostinil is a known irritant and in clinical trials has been associated with adverse events including cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis, and wheezing.
- **Hypotension and syncope:** Due to pulmonary and systemic vasodilator properties, prostacyclins may be associated with symptomatic hypotension, particularly in patients with low systemic arterial pressure. Syncope may be associated with underlying PAH disease but is also more frequently reported with the use of inhaled prostacyclins. Treatment should not be initiated in patients with low blood pressure (e.g., systolic blood pressure <85 mmHg).
- **Bleeding:** Due to inhibition of platelet aggregation, prostacyclins may be associated with an increased risk of bleeding, particularly in patients on concomitant anti-platelet or anticoagulation therapy.
- **Initial Monitoring:** Vital signs and other adverse events (e.g., airway irritation) should be monitored upon initiation of inhaled prostacyclins.

CONSIDERATIONS FOR RENEWAL

- Inhaled prostacyclins appear to provide an overall modest benefit in the treatment of PAH, though effects may be clinically meaningful in some patients. In those patients with high risk features or who are severely ill, continuous infusion of a prostacyclin (e.g., IV epoprostenol, IV or SQ treprostinil) remains the preferred therapy.
- Routine evaluation of patients by the PAH provider to assess both effectiveness and tolerability of inhaled prostacyclin therapy is mandatory; those patients with a poor response should be considered for continuous infusion.
- Provider needs to give criteria (e.g., 6MWD, NYHA Functional Class Assessment, etc.) and a timepoint (e.g., 1 month, 3 months, 6 months, or other as appropriate) for evaluation and continuation of treatment with inhaled prostacyclins prior to beginning therapy.

[a] WHO Groups for the **Clinical Classification** of Pulmonary Hypertension (Simonneau G, et al. J Am Coll Cardiol. 2009;54(1) Suppl S:S43-54.)

Group	Classification
1	Pulmonary arterial hypertension (PAH): including idiopathic (IPAH), heritable PAH, drug and toxin induced, and associated (APAH): including connective tissue diseases, congenital heart diseases, portal hypertension, HIV infection
1'	Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2	Pulmonary hypertension due to left heart disease
3	Pulmonary hypertension associated with lung diseases and/or hypoxemia
4	Pulmonary hypertension due to chronic thrombotic or embolic disease
5	Miscellaneous pulmonary hypertension (with unclear multifactorial mechanisms)

[b] WHO **Functional Classification** (modified NYHA Functional Class) (Rubin. Chest. 2004;126:7S-10S)

I	No limitation in physical activity; ordinary physical activity does not cause dyspnea or fatigue
II	Slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest
III	Marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest
IV	Unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity